REMARKS

Applicants note that claims 245, 248-251, 253-255, 260, 264, 268, 270, 270, 272, 284, 288-290, 296, 299, 303, 304, 308-313 and 318-326 are pending in the above-referenced application. Claims 318-323 have been withdrawn. Claims 288 and 289 have been canceled without prejudice to advance prosecution. Applicants do reserve the right to file subsequent continuation and/or divisional applications on canceled subject matter.

Claims 245, 260, 284, 299, 325 and 326 have been amended to more distinctly claim that which Applicants regard as the invention. These amendments have also been made to advance prosecution. Applicants do reserve the right to file subsequent continuation and/or divisional applications on any canceled subject matter. Specifically, claim 245 has been amended to more distinctly recite that the gene product in the eukaryotic cell is a sense or antisense nucleic acid and claims 260 and 284 have been amended to recite that the cell is an isolated cell.

Claims 299, 325 and 326, which are directed to multicassette constructs. Claims 299 and 326 have been amended to recite that the construct comprises at least three copies of a promoter; claim 325 has been amended to recite that the construct comprises more than one copy of an snRNA or bacteriophage promoter. Claims 299, 325 and 326 have also been amended to more clearly recite that each specific nucleic acid produced binds to different target nucleic acid sequences. These claim amendments are supported by the specification in Figures 44-47, on pages 164-167.

I. The Rejections Under 35 USC §101

Claims 260, 288 and 289 are rejected under 35 USC §101. It is asserted that the claims encompass cells, tissues, and organs in humans, as well as human organisms, which is considered to be nonstatutory subject matter.

Applicants respectfully traverse the rejection. However, in order to advance prosecution, claims 288 and 289 have been canceled. Furthermore, claims 260 and 284 have been amended to recite "An isolated cell...". The

isolated cell of claim 260 contains the composition of the present invention; claim 284 contains the construct of the present invention. Neither are products of nature. Thus, the subject matter recited in claims 260 and 284 would certainly be statutory subject matter.

In view of the above arguments, amendments of claims 260 and 284 and cancellation of claims 288 and 289, Applicants assert that the rejection of claims 260, 288 and 289 under 35 USC §101 have been overcome. Therefore, Applicants respectfully request that the rejection be withdrawn.

II. The Rejections Under 35 USC §102

Two rejections were made under 35 USC §102. These are set forth below.

A. The Rejection Over Izant

Claims 245, 248-251, 253-255, 260, 264, 265, 268, 272, 284, 288, 289, 290, 296 are rejected under 35 USC §102(b) as being anticipated by Izant (Chimeric Antisense RNAs, in Gene Regulation: Biology of Antisense RNA and DNA, pages 183-195 (Erickson, R.P and Izant, J.G., eds.; Raven Press, Ltd: New York) (1992), hereinafter "Izant". The Office Action specifically states:

> Izant ..... teaches nucleic acid compositions and cells, and a process for localizing a gene product in a eukaryotic cell ex vivo or in a culture, comprising providing an isolated primary nucleic acid construct comprising a primary nucleic acid which is a template for the synthesis of a secondary nucleic acid, which is a template for the synthesis of a gene product, which is an antisense nucleic acid and does not act as a template for the synthesis of the primary nucleic acid and further comprises a signal processing sequence which is optionally an snRNA U2 promoter comprising sequences for at least two stem loops present at the 3' end of the native snRNA, a nuclear re-importation signal, and which comprises a nucleic acid encoding an antisense nucleic acid sequence replacing stem-loop sequences in the native U2 snRNA (see entire document, esp. pages 183-184; 186-190).

Applicants respectfully traverse the rejection. Before responding to the

rejection, Applicants note that it appears that on page 5 of the Office Action, one sentence provides a mixture of various elements in each of the independent claims 245, 265 and 299 but does not describe any particular independent claim. In this response, Applicants will distinguish the subject matter recited in claim 245 and dependent claims 248-251, 253-255, 260 and 264 and subject matter recited in claim 265 and dependent claims 272, 284, 288 and 289, the claims that were the subject of the rejection.

With respect to claim 245 and dependent claims 248-251, 253-255, 260 and 264, Izant does not teach each and every element of the subject matter claimed, a primary nucleic acid that synthesizes a secondary nucleic acid, whereupon the secondary nucleic acid is used as template for synthesis of a gene product that is a tertiary nucleic acid (either a sense or antisense nucleic acid). Specifically, Izant does not give any teaching or suggestion that a tertiary nucleic acid can or should be made from a secondary nucleic acid. Further there is not any particular teaching from Izant indicate how this would be done.

Applicants with respect to claims 265 and dependent claims 272, 284, 288 and 289, take issue with the description of the Izant process as encompassing " encoding an antisense nucleic acid sequence replacing stem-loop sequences in the native U2 snRNA" (emphasis added) even after looking at the entire document as advised. In Applicants' view, there is no teaching in Izant of replacement of U2 sequences involved in stem-loop formation by antisense sequences. In Figure 1, a simple drawing shows the presence of a small antisense sequence in a portion of snRNP that lies between the 5' stem-loop and the three stem-loops at the 3' end. This picture appears to be a shorthand version of the illustration of Figure 2, entitled "Chimeric antisense U2 snRNA design". In this diagram, additional sequences were added to the native U2 sequence in order to add a restriction enzyme site for insertions into the U2 sequence: "....the mature Xenopus U2 transcript that was mutated to insert Xho restriction sites....."[1] (emphasis added). In addition to the cited text, a precise indication of the added sequences can be ascertained by a comparison of the

[1] Izant, p. 188, Figure 2 legend

Izant sequence in Figure 2 with the published sequences of Xenopus snRNA. For example, Applicants have attached hereto Pan et al., 1989, Nucl. Acids Res. 17: 6553-6568 as Appendix A, which has the sequence expressed diagrammatically in Figure 1. This comparison shows that the sequence CGUCCUCGAGGCCUCGAGGGGAUC (with the Xho sites underlined) has been added to the transcripts of the native U2 snRNA sequence by Izant. At this point it should be pointed out that there is no loss of the nucleotides that make up the normal U2 sequences and there is only the addition of a linker sequence that is then used by Izant for insertions. Various antisense sequences are subsequently added in Izant using the artificially introduced Xho sites. Since there are two Xho sites in Izant's linker sequence, a small section of Izant's artificial sequence is lost during this step. However, after addition of the new antisense sequences, an extra 17 nucleotides remain of his artificial linker and no native snRNA sequences are lost or replaced. As such, it is a mischaracterization to describe Izant "replacing" any snRNA sequences.

In view of the above arguments Applicants assert that the rejection under 35 USC §102(b) over Izant has been overcome. Therefore, Applicants respectfully request that this rejection be withdrawn.

B. Meador

Claims 245, 248-251, 253-255, 264, 272, 284, 288, 289 are rejected under 35 U.S.C. 102(e) as being anticipated by Meador et al (USPN 5,547,862) ("Meador"). The Office Action specifically states:

> Meador et al (USPN 5,547,862) teach cells and in vitro cultures comprising nucleic acid compositions comprising an isolated primary nucleic acid construct comprising a primary nucleic acid which is a template for the synthesis of a secondary nucleic acid which is a template for the synthesis of a gene product, and further comprises a signal processing sequence.

Applicants respectfully traverse the rejection. In Applicants' view, Meador does not teach all of the elements recited in claim 245 and claims which depend from claim 245, claims 248-251, 253-255, 264 and claims 272, 284, 288, 289

which depend from claim 265. The composition of claims 245, 248-251, 253-255, 264 contains a primary nucleic acid that synthesizes a secondary nucleic acid, whereupon the secondary nucleic acid is used as template for synthesis of a gene product that is a tertiary nucleic acid (either a sense or antisense nucleic acid). In contrast, the Meador reference teaches a construct (a primary nucleic acid) with two, three and even four promoters that are used to express RNA (secondary nucleic acid products) but these products are not used to synthesize tertiary products. Their secondary nucleic acid products may be templates for the synthesis of a "gene product" (as described in the Office Action) but this "gene product" is not described as being a nucleic acid, nor is there any teaching or suggestion of how such secondary nucleic acids could ever be used as templates to synthesize either sense or antisense nucleic acid "gene products".

Claims 272, 284, 288, 289 all depend from claim 265. Thus the claimed constructs would all require three elements of claim 265: a nuclear localization sequence comprising a portion of U1, U2 or U4 snRNA, said portion of U1, U2 or U4 snRNA comprising sequences for (a) at least two stem loops present at the 3' end of native U1, U2 or U4 snRNA, and (b) a reimportation signal and (ii) an antisense nucleic acid sequence, said antisense nucleic acid sequence replacing sequences that participated in stem-loop formation in the native form of said U1, U2 or U4 snRNA. Clearly, one of the essential elements of the claimed constructs is the presence of an sNRNA where some of the sequences have been replaced with anti-sense sequences. The Meador reference has no description of manipulation of snRNA with replacement with anti-sense sequences. In fact, there is no mention of snRNA at all in this reference.

In view of the above arguments, Applicants assert that the rejection over Meador has been overcome. Therefore, Applicants respectfully request that the rejection be withdrawn.

III. The Rejections Under 35 USC §103

Claims 245, 248-251, 253-255, 260, 264, 265, 268, 272, 284, 288-290, 296, 299, 303, 304, 308-313, 324-326 are rejected under 35 USC §103(a) as

being unpatentable over Meador and Izant, the combination in view of Calabretta et al. (USPN 5,734,039) ("Calabretta") and Binkley et al (Nucleic Acids Research, 1995, Vol. 23, No. 16, pages 3198-3205) ("Binkley"), the combination further in view of Craig et al (WO 95/08635) ("Craig") and Alul et al (USPN 5,532,130) ("Alul"). The Office Action specifically states:

> It would have been obvious to design a multi-cassette nucleic acid construct comprising the U2 snRNP promoter construct taught previously by Izant, and relying on the teachings of multiple promoter constructs taught previously by Meador because the elements required for producing (secondary) recombinant nucleic acids, including antisense and sense nucleic acids, using either the U2 or bacteriophage promoters were well known in the art. One would have been motivated to design and utilize such nucleic acid constructs because they provide the flexibility of expressing multiple nucleic acids encoded by operably linked primary nucleic acids, including elements that allow for localization in different subcellular compartments, depending on where the target gene is located. One would have reasonably expected that the inclusion of nuclear localizing or cytoplasmic localizing signals in the particular cassette would allow for the expression of the operably linked nucleic acid in the corresponding subcellular component. One would have been motivated to express such varied constructs in order to target and inhibit the expression of target genes in different cellular subcomponents with antisense, upon the expression of a particular antisense via a corresponding particular cassette encoding a particular, corresponding localization signal.
>
> It would have been obvious to incorporate operably linked RNA oligonucleotides that bind to proteins, as taught by Binkley, or antisense oligonucleotides taught in the system of Calabretta et al or Izant. One would have been motivated to incorporate RNA oligonucleotides that bind to proteins instead of the antisense oligonucleotides in the multicomponent system taught previously by Meador because Binkley teaches that high affinity RNA ligands can be produced that specifically bind to proteins, and can be easily generated and isolated using the SELEX procedure.

One would have a reasonable expectation of success given that each of the nucleic acid molecules were known to bind with target molecules in a sequence specific manner, as evidenced by the teachings of Calabretta, Izant, and Binkley. One would have a reasonable expectation of success to express the protein binding RNA molecules of Binkley or the dual targeting system of Calabretta in the multi-cassette system of Meador, or alternatively swapping the multi-cassette promoters of Meador with the U2 promoter taught previously by Izant, with the advantage of producing two, three or more different inhibitory or binding molecules at once, and optionally in different parts of the cell, depending on the location of the corresponding target gene.

It also would have been obvious to use the SELEX method to assay for RNA molecules that bind to a protein, as taught by Binkley and to specifically use a decoy protein as the protein, as taught by Craig. One of ordinary skill would have been motivated to design and synthesize antisense that target and inhibit the expression of HIV proteins to search for potential therapeutics to inhibit HIV infections, as taught previously by many in the art, including Alul et al. One would have been motivated to screen for resultant RNA aptamers against a decoy protein because Binkley teaches that high affinity RNA ligands to proteins can be easily isolated using the SELEX procedure and teach that such RNAs may furnish useful diagnostic tools for the study of proteins, or to regulate the actions of decoy proteins in a cell. Since teach that decoy proteins are proteins that are useful to serve as mutants capable of binding to a preferred site but yet incapable of activating transcription, one would have been motivated to use the SELEX method of Binkley. To identify RNA ligands to any known protein, such as the decoy proteins of Craig, or to screen for RNA ligands that localize and inactivate the decoy proteins in a cell.

One would have a reasonable expectation of success given that Izant and Calabretta teach the ability of antisense to bind and inhibit the expression of a target gene, Craig teaches the benefits of decoy proteins, and Binkley teach assaying for RNA aptamers using routine experimentation, and teach a method

(SELEX) that is widely use to identify RNA molecules that bind to known proteins.

Applicants respectfully traverse the rejection. Before addressing the rejection itself, Applicants wish to again clarify that there are three sets of claims. The composition recited in claim 245 and dependent claims 248-251, 253-255, 264 contains a primary nucleic acid that synthesizes a secondary nucleic acid, whereupon the secondary nucleic acid is used as template for synthesis of a gene product that is a tertiary nucleic acid (either a sense or antisense nucleic acid). As noted above, claims 265, 268, 272, 284, 288-290 and 296, would all require three elements: a nuclear localization sequence comprising a portion of U1. U2 or U4 snRNA, said portion of U1. U2 or U4 snRNA comprising sequences for (a) at least two stem loops present at the 3' end of native U1. U2 or U4 snRNA, and (b) a reimportation signal and (ii) an antisense nucleic acid sequence, said antisense nucleic acid sequence replacing sequences that participated in stem-loop formation in the native form of said U1. U2 or U4 snRNA.

Claims 299, 303, 304, 308-313 and 318-326 are directed to multicassette constructs. Claims 299, and 326 have each been amended to recite that the constructs contain at least three copies of a promoter. Claim 325 recites that the construct contains at least more than one copy of an snRNA or bacteriophage promoter. Further, the construct of claim 299 and dependent claims 303, 304, 308-313, 318-324 and claims 325-326 recited that each specific nucleic acid, each such specific nucleic acid so produced being substantially nonhomologous with each other and being either complementary with a specific portion of one or more viral RNAs (HIV RNAs in the case of claim 326) in a cell or binds to a specific viral protein (HIV protein in the case of claim 326), wherein each specific nucleic acid binds to different target nucleic acid sequences upon introduction into a eukaryotic cell.

It appears that the rejection under 35 USC §103 is directed primarily directed to the claimed multi-cassette construct. However, given that all of the pending claims are recited, Applicants will point out how each set of pending claims are not obvious over the cited references.

A. Claims 245, 248-251, 253-255, 264

As noted above, claims 245, 248-251, 253-255 and 264 are directed to a composition that contains a primary nucleic acid that synthesizes a secondary nucleic acid, whereupon the secondary nucleic acid is used as template for synthesis of a gene product that is a tertiary nucleic acid (either a sense or antisense nucleic acid). In Applicants view, these claims would not be obvious over the cited references.

The disclosures of Meador and Izant were discussed above. In summary, while Meador describes the synthesis of a gene product from a secondary nucleic acid, there is no teaching that the "gene product itself is a nucleic acid". There is only a description of primary and secondary nucleic acids in Meador. Izant describes a nucleic acid clone (a primary nucleic acid construct) which transcribes U2 RNA transcripts with anti-sense sequences embedded within them. Thus, the U2 transcripts are secondary nucleic acid products. Clearly neither Meador nor Izant teach or suggest the secondary nucleic acid acting as a template for the synthesis of a gene product which is a sense or antisense nucleic acid and does not act as a template for the synthesis of the primary nucleic acid.

The other cited references, Calabretta, Binkley, Craig and Alul would not fill in this gap. Further, these references would add nothing of significance with respect to Meador and Izant. Specifically, as noted in the Office Action, Calabretta teaches a nucleic acid construct targeting a cytoplasmic oncogene or proto-oncogene DNA, and a second segment targeting a nuclear oncogene or proto-oncogene. The DNA containing segments are in inverted orientation such that transcription of the DNA produces RNA complementary to the two mRNA transcripts of the two oncogene targets. This is significantly different from the composition recited in claims 245, 248-251, 253-255 and 264. Binkley, Craig and Alul are directed to totally different subject areas. Binkley teaches molecules that may bind to cellular protein; Craig teaches expression of a viral decoy protein; Alul discloses anti-sense sequences containing 2'-5' linkages and their

uses as therapeutics. Addition of these references would not result in the compositions recited in claims 245, 248-251, 253-255 and 264.

In summary, it is Applicants view that the combination of the cited references would not result in nor would even suggest the composition recited in claims 245, 248-251, 253-255 and 264. Thus, these claims are not obvious over the cited references and the rejection of these claims under 35 USC §103 should be withdrawn.

B. Claims 265, 268, 270, 272, 284, 288, 289, 290, 296

As noted above, claims 265, 268, 272, 284, 288-290 and 296, would all require three elements: a nuclear localization sequence comprising a portion of U1, U2 or U4 snRNA, said portion of U1, U2 or U4 snRNA comprising sequences for (a) at least two stem loops present at the 3' end of native U1. U2 or U4 snRNA, and (b) a reimportation signal and (ii) an antisense nucleic acid sequence, said antisense nucleic acid sequence replacing sequences that participated in stem-loop formation in the native form of said U1, U2 or U4 snRNA. Claims 288 and 289 have been canceled with out prejudice. In Applicants view, the remaining pending claims would not be obvious over the cited references.

The disclosures of Meador and Izant were discussed above. As noted above, Meador has no description of snRNA at all. Further, Meador does not teach or suggest replacing native sequences with anti-sense sequences. Izant, *contra* to assertions made in the Office Action, does not describe the replacement of U2 sequences with anti-sense sequences. As noted in the response to the rejection under 35 USC §102, there is no loss of the nucleotides that make up the normal U2 sequences; there is only the addition of a linker sequence that is then used by Izant for insertions. Further, there is no suggestion of actually **replacing** U2 sequences with anti-sense sequences.

The other cited references, Calabretta, Binkley, Craig and Alul would not add anything of significance. None of these references are related to snRNA sequences or replacing any stem-loop sequences.

In summary, only one of the cited references, Izant, even has any disclosure remotely relating to snRNA. That reference only discloses adding sequences to a construct containing U2 sequences. None of the references would fill in the gap.

In view of the above arguments and the cancellation of claims 288 and 289, Applicants assert that the rejection of claims 265, 268, 272, 284, 288-290 and 296 under 35 USC §103 have been overcome. Therefore, Applicants respectfully request that the rejection of these claims under 35 USC §103 be withdrawn.

C. Claims 299, 303, 304, 308-313 and 318-326

Claims 299, 303, 304, 308-313 and 318-326 are directed to multicassette constructs. Claims 299 and 326 have each been amended to recite that the constructs contain at least three copies of a promoter. Claim 325 recites that the construct contains at least more than one copy of an snRNA or bacteriophage promoter.

Contra to the assertions in the Office Action, it would not have been obvious to design a multi-cassette nucleic acid construct comprising the U2 snRNP promoter construct taught previously by Izant, and relying on the teachings of multiple promoter constructs taught previously by Meador. Although Meador does teach a vector containing multiple promoters, the multiple promoter system of Meador consists of different promoters. There is no description of the use of multiple copies of the same promoter, a feature of amended claims 299, 325 and 326. Further, as conceded in the Office Action on page 7:

> The primary references do not teach the expression of antisense specific for targets in two different subcellular locations, nor do they teach nucleic acids that bind to or target nucleic acids encoding HIV cellular proteins, nor nucleic acids that bind to decoy proteins.

Izant does not teach a vector containing multiple promoters or even multiple copies of the same promoter. It merely teaches an snRNA promoter. Further, to supplement assertions made in the Office Action, neither of the cited

primary references teaches or suggests that the multi-cassette construct produces at least one specific nucleic acid from each of the promoters, where the nucleic acids produced (a) are substantially nonhomologous with each other and are complementary with a specific portion of one or more viral RNAs in a cell or binds to a specific viral protein and (b) binds to different target nucleic acid sequences upon introduction into a eukaryotic cell.

Calabretta, one of the other references cited, concerns a method where there is transcription directed towards each of the two cellular compartments of a eucaryotic cell: the nucleus and the cytoplasm. Although Calabretta clearly describes the use of two promoters, no particular motivation exists for a construct with three separate promoters since there is no third cellular compartment in a eucaryotic cell. When more than one cytoplasmic RNA target is desired to be targeted, the standard methodology at the time of Calabretta (and even at the time of the filing of the present invention) was to construct a multivalent transcript; i.e, a single transcript with multiple anti-sense sequences fused together. As such, a desire to use the method of Calabretta for multiple cytoplasmic targets and multiple nuclear targets would result in a construct that directed transcription of a multivalent cytoplasmic transcript and a multivalent nuclear transcript. Further, Calabretta teaches the use of two different promoters not multiple copies of the same promoter.

Binkley and Craig merely provide discussions of what particular targets a transcript made from a promoter may use as a target. Neither reference provides any particular encouragement for the use of three promoters or for "swapping multiple promoters of Meador for the U2 promoter of Izant"[2].

Alul merely discloses anti-sense sequences containing 2'-5' linkages and their uses as therapeutics. The Background of the Invention in Alul merely summarizes the state of the art with respect to the effect of various oligonucleotide analogs on gene expression. However, in Applicants' view, it would not have been obvious to combine Alul with the other cited references since the 2'-5' oligonucleotides are not incorporated into constructs but are used

[2] See Office Action, p. 9

as stand alone therapeutics. The claims recite a construct that would be used as a template for synthesis when present in a cell. It is difficult to imagine circumstances where incorporation of the 2'-5' nucleotides of AluI would take place within a cell.

In view of the above arguments, Applicants assert that the rejections of all of the pending claims under 35 USC §103 have been overcome. Therefore, Applicants respectfully request that the rejections be withdrawn.

IV. The Rejections Under 35 USC §112, Written Description

Claims 245, 248-251, 253-255, 260, 264, 265, 268, 270, 272, 284, 288-290, 296, 299, 303, 304, 308-313, 325 and 326 have been rejected under 35 U.S.C. 112, first paragraph. The Office Action specifically states on page 11:

> The specification and claims do not adequately describe the various genera comprising i.) any snRNA comprising sequences for stem loops present at the 3' end of any native snRNA, and which comprise any re-importation signal or which comprise any antisense replacing sequences that participated in stem-loop formation in the native form of any snRNA; ii.) any cellular protein comprising any nuclear localizing protein or cytoplasmic localizing protein; iii.) any decoy protein binding to any protein required for viral assembly or viral replication.

Applicants respectfully traverse. As noted in previous responses, Applicants disagree with the assertion that there is "broad genera" being described since U1, U2 and U4 are the only snRNA species being recited. The native sequences of these U1, U2 and U4 RNA species comprise stem-loop structures and their own particular nuclear re-importation signals, which were well known and described in the literature at the time of the filing. Further, the identification of the sequences that are required for appropriate stable expression and for reimportation were actually based upon numerous mutation and deletion studies carried out prior to disclosure of the present invention. As such, knowledge of the nature of sequences that could be deleted was widely known in the field at large as well as by the Applicants. In Applicants' view, although only

U1 was used, there would be a minimal amount of effort required to apply the present methods to U2 or U4.

The Office Action further asserts on page 13:

> Contrary to Applicant's assertions, the instant disclosure, at the time of filing, does not provide enough description of an adequate number of species for the broad genera claimed, and purported secondary structure consensus does not ensure the generation of functioning expression cassettes for all of the species claimed. The example provided in the instant disclosure does not fill the gap of information needed about what deletions would be tolerated in the snRNA structures and still allow for retaining the features of promoter function and nuclear re-importation activities. Applicant was therefore not in possession of this information at the time of filing the instant disclosure, and the art does not supplement this deficiency. The specification teaches the human U1 operon, and elimination of 49 base sequences involved in the formation of A and B loops formed by U1. Adequate written description has been provided for the species described by the particular construct described in example 26, exemplified in Figure 41, and provided in the sequence of Figure 42. The specification also teaches three segment, triple operon constructs comprising either three U1 promoters or three T7 promoters, and antisense targeting HIV 5' common leader, the TAT/REV coding sequence and the splice acceptor site for TAT/REV of HIV.
>
> The disclosure of these constructs, however, is insufficient to teach or adequately describe a representative number of species for the broad genera of nucleic acid constructs claimed, such that the common attributes or characteristics concisely identifying members of each proposed genus are exemplified, and further whereby any primary nucleic acid construct comprising any primary nucleic acid sequence is introduced into any eukaryotic cells and acts as a template for the synthesis of any secondary nucleic acid for the synthesis of any gene product, which nucleic acid construct comprises any snRNA comprising sequences for stem loops present at the 3' end of any native snRNA, and which comprise any re-

importation signal or which comprise any antisense replacing sequences that participated in stem-loop formation in the native form of any snRNA; ii.) any cellular protein comprising any nuclear localizing protein or cytoplasmic localizing protein; iii.) any decoy protein binding to any protein required for viral assembly or viral replication. The general knowledge and level of skill in the art at the time of filing do not supplement the omitted description because specific, not general, guidance is what is needed to provide a representative number of species for the broad array of nucleic acid constructs claimed.

Applicants traverse. In Applicants' view, there is more than adequate written description of the subject matter recited in claims 245 and dependent claims 246-255, 260 and 264. Specific examples of production centers are provided in Figures 36-40. A description of Figures 36-40 is provided in Examples 22 (Describes Figure 36); Example 23 (describes Figures 37 and 38), Example 24 (describes Figure 39) and Example 25 (describes Figure 40).

With respect to claim 265, as noted above, the exemplification provided by U1 in Example 26 allows the utilization of other U1 sequences without any particular difficulties or undue experimentation. The same is true for adapting the present teachings to U2 or U4; the structure and roles of the various sequences of U1, U2 and U4 were well known in the literature at the time of the filing, such that the choice of sequences to be deleted for replacement purposes is a minor exercise that is easily and predictably done by one skilled in the art. With regard to the choice of sequences that are put into snRNA as anti-sense, there is no particular need for describing and creating novel sequences as ones that have been described in the literature are perfectly suitable. As described in the specification itself, two out of the three sequences were taken from the anti-sense literature and any other of a variety of sequences could have been used instead with a strong likelihood of success.

A similar situation exists with regard to multi-promoter cassettes of the present invention (see claims 299, 303-304, 308, 312-313, 325-326) where the use of various combinations of antisense, cellular proteins or decoy proteins, can be adapted from the literature. The only change that is being introduced is that

instead of being expressed individually, they are now part of a multi-expression construct, a situation that should not alter their individual effectiveness. Consequently it is the belief of Applicants that "any" antisense that has been previously shown to be effective can be used in the present invention with U1, U2 or U4 snRNA as long as it is small enough to work as a replacement and that "any" antisense, "any" cellular protein, and "any" decoy protein should work with a multimeric promoter cassette construct of the present invention as long as it has been shown to work with a single individual promoter construct.

Applicants with respect to claims 299, 303, 304, 308-313, and 325-326, further note that claims 299 and 326 have been amended to recite that the construct comprises at least three copies of a promoter. Claim 325 has been amended to recite that the construct comprises at least one copy of a promoter. Adequate guidance in Applicants view is provided in the specification and in the art for choosing a promoter. Specifically, pages 109-110 state:

> Intracellular synthesis of product entities can be controlled by the choice of promoter or initiating element. Thus, a cassette can be designed which contains sequences for a product entity whose synthesis is under control of an inducible promoter providing for temporal synthesis of product entities. This provides advantages to applications wherein, for example, constant production of the product entity would have deleterious effects for the host cell or organism, but whose short term effects are beneficial. For example, induction of a product entity which arrests cell division processes can impart to the cell virus resistance where virus replication is dependent on such cellular processes. In order to restore the cellular processes at a later time, induction can be terminated. Induction can be mediated by use of promoters which can be induced by small molecules such as antibiotics, hormones and heavy metals such as zinc. Alternatively, in cases where constant production of a product entity or entities is beneficial, a promoter not subject to induction can be utilized.
>
> Promoters can also be chosen on the basis of their efficiency. In cases where high levels of product entities are required promoters which initiate transcription at a high frequency can be utilized.

Alternatively, when lower levels of product entities are desirable less efficient promoters can be used.

Insertion of appropriate sequences are taught in Examples 27-29. Furthermore, the insertion of appropriate sequences could be accomplished by a variety of methods besides the methods actually employed.

In view of the above arguments the rejections under 35 USC §112, first paragraph (written description) have been overcome. Therefore, Applicants respectfully request that the rejections be withdrawn.

SUMMARY AND CONCLUSIONS

It is Applicants belief that the pending claims are in condition for allowance. However, if a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney request that he be contacted at the number provided below.

Respectfully submitted,

/Cheryl H Agris/

Dated: May 5, 2010

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